REMARKS

Reconsideration of the application is requested in view of the amendment to the claims and the remarks presented herein.

The claims in the application are claims 1 to 7 and 9 to 16, all other claims being cancelled.

Claims 1 to 15 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite in the term "nucleofugal organic group" which the Examiner deems not to be standard chemical term. The Examiner agrees with IUPAC's definition of nucleofugal but deems Applicants'definition as being confusing by using "halogen or" with the term. The Examiner agrees that halogen falls with the term.

Applicants respectfully traverse this ground of rejection in view of the Examiner's agreement with IUPAC that the term nucleofugal organic group includes halogens. The specification and claims have been amended to clarify the definition to conform to everyone's agreement with this definition so that halogen is clearly within the scope of nucleofugal as agreed by the Examiner.

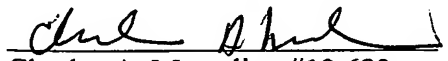
Applicants are submitting copies of pages 293 and 352 to 357 of the Advance Organic Chemistry to explain that in RN_2^+ that the nucleofugal portion is N_2 and not the

entire RN_2^+ group. Therefore, it is now believed clear what is encompassed by the art recognized term nucleofugal organic group and withdrawal of this rejection is requested.

Applicants have cancelled Claim 8 and added Claim 16 to define R_3 as being halogen, mesylate and tosylate as set forth on page 5 of the specification.

In view of the amendments to the specification and the claims, it is believed that the claims point out Applicants'patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Hedman and Costigan



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Enclosures

10

ALIPHATIC NUCLEOPHILIC SUBSTITUTION

In nucleophilic substitution the attacking reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:

$$R\overset{\curvearrowright}{-}X + \overline{Y} \longrightarrow R-Y + \overline{X}$$

This equation says nothing about charges. Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are

Type I	$R-I + OH^-$	$\longrightarrow R-OH + I^-$
Type II	$R-I + NMe_3$	$\longrightarrow R-\overset{\oplus}{N}Me_3 + I^-$
Type III	$R-\overset{\oplus}{N}Me_3 + OH^-$	$\longrightarrow R-OH + NMe_3$
Type IV	$R-\overset{\oplus}{N}Me_3 + H_2S$	$\longrightarrow R-\overset{\oplus}{S}H_2 + NMe_3$

In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe_3 is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.[1] By far the most common are the SN1 and SN2 mechanisms.

[1]For a monograph on this subject, see Hartshorn *Aliphatic Nucleophilic Substitution*; Cambridge University Press: Cambridge, 1973. For reviews, see Katritzky; Brycki *Chem. Soc. Rev.* **1990**, *19*, 83-105; Richard *Adv. Carbocation Chem.* **1989**, *1*, 121-169; Bazilevskii; Koldobskii; Tikhomirov *Russ. Chem. Rev.* **1986**, *55*, 948-965; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley: New York, 1973, pp. 409-490. For some older books, see Thornton *Solvolysis Mechanisms*; Ronald Press: New York, 1964; Bunton *Nucleophilic Substitution at a Saturated Carbon Atom*; American Elsevier: New York, 1963; Streitwieser *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962.

are not completely understood. Several possible explanations have been offered.[325] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[326] another is that the transition state is stabilized by the extra pair of electrons;[327] a third is that the adjacent electron pair reduces solvation of the nucleophile.[328] Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,[329] though HO_2^- shows a strong alpha effect in solution. The alpha effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[330] and for reactions of a nucleophile with a carbocation,[331] but is generally smaller or absent entirely for substitution at a saturated carbon.[332]

The Effect of the Leaving Group

1. *At a saturated carbon.* The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$.[333] Reactions in which the leaving group does not come off until it has been protonated have been called SN1cA or SN2cA, depending on whether after protonation the reaction is an SN1 or SN2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $A_h + D_N + A_N$ and $A_h + A_ND_N$; that is, the same designations as SN1 and SN2, with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in super-acid solutions.[334] At higher temperatures they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^-, OH^-) cannot take part in SN1cA or SN2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[335] Because SN1 reactions do not require powerful nucleophiles but do require good leaving groups, most of them take place under

[325]For discussions, see Wolfe; Mitchell; Schlegel; Minot; Eisenstein *Tetrahedron Lett.* **1982,** *23*, 615; Hoz; Buncel *Isr. J. Chem.* **1985,** *26*, 313.

[326]Buncel; Hoz *Tetrahedron Lett.* **1983,** *24*, 4777. For evidence that this is not the sole cause, see Oae; Kadoma *Can. J. Chem.* **1986,** *64*, 1184.

[327]See Hoz *J. Org. Chem.* **1982,** *47*, 3545; Laloi-Diard; Verchere; Gosselin; Terrier *Tetrahedron Lett.* **1984,** *25*, 1267.

[328]For other explanations, see Hudson; Hansell; Wolfe; Mitchell *J. Chem. Soc., Chem. Commun.* **1985,** 1406; Shustov *Doklad. Chem.* **1985,** *280*, 80. For a discussion, see Herschlag; Jencks *J. Am. Chem. Soc.* **1990,** *112*, 1951.

[329]DePuy; Della; Filley; Grabowski; Bierbaum *J. Am. Chem. Soc.* **1983,** *105*, 2481; Buncel; Um *J. Chem. Soc., Chem. Commun.* **1986,** 595; Terrier; Degorre; Kiffer; Laloi *Bull. Soc. Chim. Fr.* **1988,** 415. For some evidence against this explanation, see Moss; Swarup; Ganguli *J. Chem. Soc., Chem. Commun.* **1987,** 860.

[330]For example, see Kice; Legan *J. Am. Chem. Soc.* **1973,** *95*, 3912.

[331]Dixon; Bruice *J. Am. Chem. Soc.* **1971,** *93*, 3248, 6592.

[332]Gregory; Bruice *J. Am. Chem. Soc.* **1967,** *89*, 4400; Oae; Kadoma; Yano *Bull. Chem. Soc. Jpn.* **1969,** *42*, 1110; McIsaac; Subbaraman; Subbaraman; Mulhausen; Behrman *J. Org. Chem.* **1972,** *37*, 1037. See, however, Beale *J. Org. Chem.* **1972,** *37*, 3871; Buncel; Wilson; Chuaqui *J. Am. Chem. Soc.* **1982,** *104*, 4896, *Int. J. Chem. Kinet.* **1982,** *14*, 823.

[333]For a review of ORH^+ as a leaving group, see Staude; Patat, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 22-46.

[334]Olah; O'Brien *J. Am. Chem. Soc.* **1967,** *89*, 1725; Olah; Sommer; Namanworth *J. Am. Chem. Soc.* **1967,** *89*, 3576; Olah; Olah, in Olah; Schleyer, Ref. 92, vol. 2, 1970, pp. 743-747.

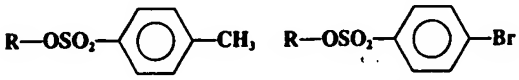
[335]Even in the gas phase, NH_3 takes a proton from $CH_3OH_2^+$ rather than acting as a nucleophile: Okada; Abe; Taniguchi; Yamabe *J. Chem. Soc., Chem. Commun.* **1989,** 610.

acidic conditions. In contrast, SN2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides[336] are cleaved quite easily and protonated epoxides even more easily. Aziridines[337] and epi-

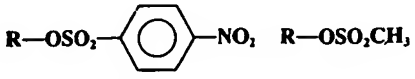
sulfides, three-membered rings containing, respectively, nitrogen and sulfur, are also easily cleaved (see p. 368).[338]

Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate, brosylate, nosylate,* and *mesylate* are better leaving groups



ROTs — *p*-Toluenesulfonates, Tosylates

ROBs — *p*-Bromobenzenesulfonates, Brosylates



RONs — *p*-Nitrobenzenesulfonates, Nosylates

ROMs — Methanesulfonates, Mesylates

than halides and are frequently used. Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[339] alkyl perchlorates ($ROClO_3$),[340] ammonioalkanesulfonate esters (*betylates*) ($ROSO_2(CH_2)_nNMe_3^+$),[341] alkyl fluorosulfonates ($ROSO_2F$),[342] and the fluorinated com-

[336]For a review of the reactions of epoxides, see Smith *Synthesis* **1984,** 629-656. For a review of their synthesis and reactions, see Bartók; Láng, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 609-681.

[337]For a review of aziridine cleavages in the synthesis of natural products, see Kametani; Honda *Adv. Heterocycl. Chem.* **1986,** *39,* 181-236.

[338]There is evidence that relief of ring strain is not the only factor responsible for the high rates of ring-opening of 3-membered rings: Di Vona; Illuminati; Lillocci *J. Chem. Soc., Perkin Trans. 2* **1985,** 1943; Bury; Earl; Stirling *J. Chem. Soc., Chem. Commun.* **1985,** 393.

[339]For a monograph, see Perst, Ref. 84. For reviews, see Perst, in Olah; Schleyer, Ref. 92, vol. 5, 1976, pp. 1961-2047; Granik; Pyatin; Glushkov *Russ. Chem. Rev.* **1971,** *40,* 747-759. For a discussion of their use, see Curphey *Org. Synth.* **VI,** 1021.

[340]Baum; Beard *J. Am. Chem. Soc.* **1974,** *96,* 3233. See also Kevill; Lin *Tetrahedron Lett.* **1978,** 949.

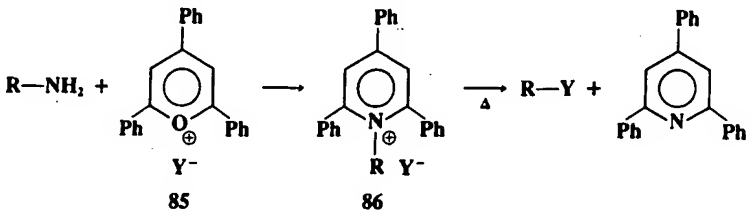
[341]King; Loosmore; Aslam; Lock; McGarrity *J. Am. Chem. Soc.* **1982,** *104,* 7108; King; Lee *Can. J. Chem.* **1981,** *59,* 356, 362; King; Skonieczny; Poole *Can. J. Chem.* **1983,** *61,* 235.

[342]Ahmed; Alder; James; Sinnott; Whiting *Chem. Commun.* **1968,** 1533; Ahmed; Alder *Chem. Commun.* **1969,** 1389; Alder *Chem. Ind. (London)* **1973,** 983. For a discussion of the hazards involved in the use of these and other alkylating agents, see Alder; Sinnott; Whiting; Evans *Chem. Br.* **1978,** 324.

pounds *triflates*[343] and *nonaflates*.[343] *Tresylates* are about 400 times less reactive than triflates, but still about 100 times more reactive than tosylates.[344] Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in super-acid solutions (p. 312) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[345] Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

$R—OSO_2CF_3$	$R—OSO_2C_4F_9$	$R—OSO_2CH_2CF_3$
ROTf	Nonafluorobutanesulfonates	2,2,2-Trifluoroethanesulfonates
Trifluoromethanesulfonates	Nonaflates	Tresylates
Triflates		

NH_2, NHR, and NR_2 are extremely poor leaving groups,[346] but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate $RNTs_2$. The NTs_2 group has been successfully replaced by a number of nucleophiles.[347] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.[348] In this method the amine is converted to a pyridinium compound (**86**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **85**).[349] When the salt is heated, the counterion acts as a nucleophile. In some cases a



nonnucleophilic ion such as BF_4^- is used as the counterion for the conversion **85** → **86**, and then Y^- is added to **86**. Among the nucleophiles that have been used successfully in this reaction are I^-, Br^-, Cl^-, F^-, OAc^-, N_3^-, NHR_2, and H^-. Ordinary NR_2 groups are good leaving groups when the substrate is a Mannich base (these are compounds of the form $RCOCH_2CH_2NR_2$; see reaction **6-16**).[350] The elimination-addition mechanism applies in this case.

[343]For reviews of triflates, nonaflates, and other fluorinated ester leaving groups, see Stang; Hanack; Subramanian *Synthesis* **1982**, 85-126; Howells; Mc Cown *Chem. Rev.* **1977**, *77*, 69-92, pp. 85-87.

[344]Crossland; Wells; Shiner *J. Am. Chem. Soc.* **1971**, *93*, 4217.

[345]Peterson; Clifford; Slama, Ref. 89; Olah; DeMember; Schlosberg; Halpern *J. Am. Chem. Soc.* **1972**, *94*, 156; Peterson; Waller *J. Am. Chem. Soc.* **1972**, *94*, 5024; Olah; Svoboda *Synthesis* **1973**, 203; Olah; Mo *J. Am. Chem. Soc.* **1974**, *96*, 3560.

[346]For a review of the deamination of amines, see Baumgarten; Curtis, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 929-997.

[347]For references, see Müller; Thi *Helv. Chim. Acta* **1980**, *63*, 2168; Curtis; Knutson; Baumgarten *Tetrahedron Lett.* **1981**, *22*, 199.

[348]For reviews, see Katritzky; Marson *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 420-429 [*Angew. Chem. 96*, 403-413]; Katritzky *Tetrahedron* **1980**, *36*, 679-699. For reviews of the use of such leaving groups to study mechanistic questions, see Katritzky; Sakizadeh; Musumarra *Heterocycles* **1985**, *23*, 1765-1813; Katritzky; Musumarra *Chem. Soc. Rev.* **1984**, *13*, 47-68.

[349]For discussions of the mechanism, see Katritzky; Brycki *J. Am. Chem. Soc.* **1986**, *108*, 7295, and other papers in this series.

[350]For a review of Mannich bases, see Tramontini *Synthesis* **1973**, 703-775.

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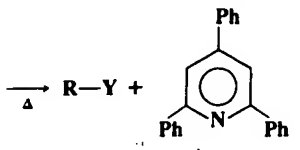

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use of such leaving groups to study mechanistic
23, 1765-1813; Katritzky; Musumarra *Chem. Soc.*

n. Chem. Soc. **1986**, *108*, 7295, and other papers

, 703-775.

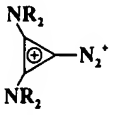
Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[351] of which the two most important are the treatment of primary amines with nitrous acid (see p. 635 for this reaction)

$$RNH_2 + HONO \longrightarrow RN_2^+$$

and the protonation of diazo compounds[352]

$$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are usually too unstable to be isolable,[353] reacting presumably by the SN1 or SN2 mechanism.[354] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[355] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, etc. as carbocations generated in other SN1 reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[356] as have ion pairs, in which OH^- (or OAc^-, etc., depending on how the diazonium ion is generated) is the counterion.[357] One class of aliphatic diazonium salts of which several members have been isolated as stable salts are the cyclopropeniumyldiazonium salts:[358]



X^- R = Me or i-Pr
X^- = BF_4^- or $SbCl_6^-$

Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[359]

[351]For reviews, see Kirmse *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 251-261 [*Angew. Chem.* *88*, 273-283]; Collins *Acc. Chem. Res.* **1971**, *4*, 315-322; Moss *Chem. Eng. News* **1971**, *49*, 28-36 (No. 48, Nov. 22).

[352]For a treatise, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986. For reviews of the reactions of aliphatic diazo compounds with acids, see Hegarty, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 2; Wiley: New York, 1978, pp. 511-591, pp. 571-575; More O'Ferrall *Adv. Phys. Org. Chem.* **1967**, *5*, 331-399. For review of the structures of these compounds, see Studzinskii; Korobitsyna *Russ. Chem. Rev.* **1970**, *39*, 834-843.

[353]*Aromatic* diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared (see also Ref. 358). For reviews see Laali; Olah *Rev. Chem. Intermed.* **1985**, *6*, 237-253; Bott, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 671-697; Bott *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 259-265 [*Angew. Chem.* *91*, 279-285]. The simplest aliphatic diazonium ion $CH_3N_2^+$ has been prepared at −120° in super-acid solution, where it lived long enough for an nmr spectrum to be taken: Berner; McGarrity *J. Am. Chem. Soc.* **1979**, *101*, 3135.

[354]For an example of a diazonium ion reacting by an SN2 mechanism, see Mohrig; Keegstra; Maverick; Roberts; Wells *J. Chem. Soc., Chem. Commun.* **1974**, 780.

[355]For reviews of the mechanism, see Manuilov; Barkhash *Russ. Chem. Rev.* **1990**, *59*, 179-192; Saunders; Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973, pp. 280-317; in Olah; Schleyer, Ref. 92, vol. 2, **1970**, the articles by Keating; Skell, pp. 573-653; and by Friedman, pp. 655-713; White; Woodcock, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 440-483; Ref. 351.

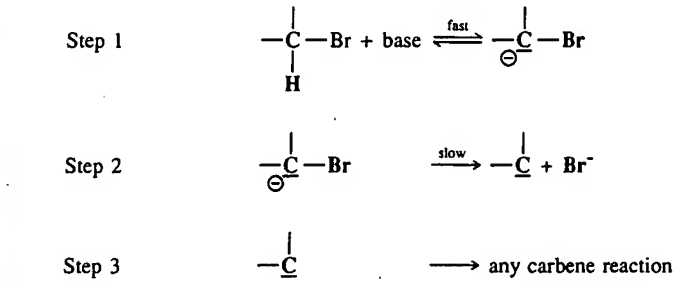
[356]Semenow; Shih; Young *J. Am. Chem. Soc.* **1958**, *80*, 5472. For a review of "hot" or "free" carbocations, see Keating; Skell, Ref. 355.

[357]Collins, Ref. 351; Collins; Benjamin *J. Org. Chem.* **1972**, *37*, 4358; White; Field *J. Am. Chem. Soc.* **1975**, *97*, 2148; Cohen; Daniewski; Solash *J. Org. Chem.* **1980**, *45*, 2847; Maskill; Thompson; Wilson *J. Chem. Soc., Perkin Trans. 2* **1984**, 1693; Connor; Maskill *Bull. Soc. Chim. Fr.* **1988**, 342.

[358]Weiss; Wagner; Priesner; Macheleid *J. Am. Chem. Soc.* **1985**, *107*, 4491.

[359]Whitmore; Langlois *J. Am. Chem. Soc.* **1932**, *54*, 3441; Streitwieser; Schaeffer *J. Am. Chem. Soc.* **1957**, *79*, 2888.

In the SN1cA and SN2cA mechanisms (p. 352) there is a preliminary step, the addition of a proton, before the normal SN1 or SN2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 199). When the net result is substitution, this mechanism has been called the SN1cB (for conjugate base) mechanism.[360] Though the slow step is an SN1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.10 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for SN1 and SN2 reactions.

2. *At a carbonyl carbon.* In both the SN1 and SN2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **67** (p. 331) there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **67** will revert to the starting compounds. Thus there is a partitioning factor between **67** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[361] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

[360]Pearson; Edgington *J. Am. Chem. Soc.* **1962**, *84*, 4607.

[361]RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

TABLE 10.10 Leaving groups listed in approximate order of decreasing ability to leave. Groups that are common leaving groups at saturated and carbonyl carbons are indicated

	Common leaving groups	
Substrate RX	**At saturated carbon**	**At carbonyl carbon**
RN_2^+	×	
ROR_2^+		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	×	
$ROSO_2F$		
ROTs, etc.[a]	×	
RI	×	
RBr	×	
ROH_2^+	× (conjugate acid of alcohol)	
RCl	×	× (acyl halides)
$RORH^+$	× (conjugate acid of ether)	
$RONO_2$, etc.[a]		
RSR_2^+[363]		
RNR_3^+	×	
RF		
ROCOR'[364]	×	× (anhydrides)
RNH_3^+		× (aryl esters)
ROAr[365]		× (carboxylic acids)
ROH		× (alkyl esters)
ROR		
RH		× (amides)
RNH_2		
RAr		
RR		

[a]ROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, etc. $RONO_2$, etc., includes inorganic ester leaving groups, such as $ROPO(OH)_2$, $ROB(OH)_2$, etc.

The Effect of the Reaction Medium[362]

The effect of solvent polarity on the rate of SN1 reactions depends on whether the substrate is neutral or positively charged. For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.11[366]) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and

[362]For a monograph, see Reichardt *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988. For reviews, see Klumpp, Ref. 294, pp. 186-203; Bentley; Schleyer *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.

[363]For a review of the reactions of sulfonium salts, see Knipe, in Stirling *The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 313-385. See also Badet; Julia; Lefebvre *Bull. Soc. Chim. Fr.* **1984**, II-431.

[364]For a review of SN2 reactions of carboxylic esters, where the leaving group is OCOR', see McMurry *Org. React.* **1976**, *24*, 187-224.

[365]Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-$ROC_6H_2(NO_2)_3$] react at rates comparable to tosylates: Sinnott; Whiting *J. Chem. Soc. B* **1971**, 965. See also Page; Pritt; Whiting *J. Chem. Soc., Perkin Trans. 2* **1972**, 906.

[366]This analysis is due to Ingold *Structure and Mechanism in Organic Chemistry*, 2d ed.; Cornell University Press: Ithaca, NY, 1969, pp. 457-463.

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